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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/849,869	05/04/2001	David J. Anderson	CALTE.004C1	1088

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EXAMINER	
ULM, JOHN D	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/849,869	ANDERSON ET AL.	
	Examiner	Art Unit	
	John D. Ulm	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-61,66-81 and 87-95* is/are pending in the application.

4a) Of the above claim(s) *92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-61, 66-81, 87-91 93-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1) Claims 57 to 61, 66 to 81 and 87 to 95 are pending in the instant application. Claims 57, 66 and 75 have been amended, claims 1 to 56, 62 to 65 and 82 to 86 have been canceled, and claims 87 to 95 have been added as requested by Applicant in the correspondence filed 15 July of 2004.

2) Newly submitted claim 92 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 92 is drawn to a compound of unspecified constitution that is neither made by nor used in the analytical process that is the elected invention. Therefore, that compound is unrelated to the process that is the elected invention.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 92 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3) The information disclosure statement filed 15 July of 2004 fails to comply with 37 CFR 1.97(c) because it lacks the fee set forth in 37 CFR 1.17(p). It has been placed in the application file, but the information referred to therein has not been considered.

4) Any objection or rejection of record that is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

5) The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6) Claims 57 to 61, 66 to 81, 87 to 91 and 93 to 95 are rejected under 35 U.S.C. § 101 because they are drawn to an invention with no apparent or disclosed specific and substantial credible utility for those reasons of record as applied to claims 57 to 61 and 66 to 83 in section 4 of the previous office action. As stated therein, these claims are drawn to a method of identifying ligands, agonists and antagonists of a "Mrg polypeptide", and specifically a "Mrg X1" polypeptide comprising the amino acid sequence presented in SEQ ID NO:16 of the instant application. The instant specification discloses that the elected Mrg X protein is a human G protein-coupled receptor that is expressed in the dorsal root ganglia (DRG), but it does not disclose a **specific** biological role for this protein or its significance to a particular disease, disorder of physiological process which one would wish to manipulate for a desired clinical effect by administering a compound that has been identified by the claimed method.

Applicant's traversal of this rejection refers to utilities for "Mrg X", as was discussed in the original rejection. The declaration by David L. Anderson refers to "Mrg X1". It is noted that the elected invention is a method that employs a protein comprising the amino acid sequence presented in SEQ ID NO:16 of the instant application, which is identified on page 13 therein as "Mrg X1". Because the elected invention relates to SEQ ID NO:16, all arguments and rejections that discuss "MrgX" or "MrgX1" are presumed to be referring to "Mrg X1" unless indicated otherwise.

Applicant has traversed this rejection on the premise that the "disclosed utility relates to the use of a specific receptor to screen for compounds that modulate

pain sensation". Applicant has provided a declaration by David L. Anderson under 37 C.F.R. 1.132 asserting that "[b]ased solely on the results presented in paragraphs 2-8" of the declaration, "it is my considered scientific opinion that MrgXI is a G protein-coupled receptor that is involved in pain signaling and could be used to identify compounds that modulate pain sensation".

The fact that SEQ ID NO:16 is the amino acid sequence of a human protein that is, more likely than not, a member of the G protein-coupled receptor family is not in dispute. The fact that the instant specification describes no less that eight different murine G protein-coupled receptors that appear to be expressed exclusively in nociceptive neurons is not disputed. Applicant's assertion that "Mrg X1" is a human ortholog of one of those eight murine receptors has been accepted. However, the claimed assay lacks specific utility in currently available form because the instant specification does not disclose with particularity how "Mrg X1" "is involved in pain signaling". Specifically, the specification does not disclose how an agonist or antagonist would effect nociception. The assertion that "Mrg X1" can be employed in the claimed assay to identify agonists and antagonists thereto because it "modulates" nociception is not an assertion of a specific utility. A compound would "modulate pain sensation" if it induced a sensation of pain or if it blocked that sensation. The specification leaves it to the practitioner of the art to first identify an agonist of "Mrg X1" and then to determine if that agonist causes analgesia or a sensation of pain when administered to an organism. To employ an assay of the instant invention in the identification of substances that inhibit or induce "Mrg X1" activity is clearly to use that protein as the object of further

research that has been determined by the courts to be a utility, which alone does not support patentability. As indicated in the previous office action, an invention must have a specific and substantial utility "in currently available form", which precludes the need for further research if that research is needed to establish a utility for the claimed invention.

Applicant urges that they have "demonstrated that Mrg receptors are activated by several classes of N-amide neuropeptides, which are known to mediate analgesia (Example 5, page 100)". On the contrary, there is absolutely no evidence of record that demonstrates that "Mrg X1' was known to be activated by any one particular compound at the time that the instant application was filed. Further, the table presented on page 104 of the instant specification shows that the activity of one compound on a specific Mrg protein is not predictive of the action of that compound on all Mrg proteins.

Applicant has relied upon the Lembo et al. publication to demonstrate that SNSR4, which is greater than 90% identical to MrgX1, is expressed exclusively in human DRG (Nature Neuroscience 5:201-209 (2002) and activated by the opioid-type ligand BAM-22. It is noted that the instant specification does not appear to have disclosed this information. An invention must be patentable at the time that an application is filed. Applicant may not rely upon subsequent discoveries by themselves or others to complete the claimed invention. In the decision *In re Lundberg*, 117 USPQ 190, 1958, the CCPA held that "advantages which are not disclosed in application cannot be urged as basis for allowing claims".

It is unclear from the record if the activities of Mrg A1 are expected to be specifically predictive of Mrg X1. The instant specification does not appear to disclose a special relationship between these two proteins relative to the plurality of other Mrg proteins described therein. Further, it is unclear from the record if it is the position of Applicant that the stimulation of Mrg X1 produces a sensation of pain or blocks such sensations. Applicant needs to clarify these two issues by identifying those portions of the specification that explain the relationship between Mrg A1 and Mrg X1, and the specific relationship between the activation of Mrg X1 and the sensation of pain. If one can not predict, by following the guidance provided by the instant specification, whether an agonist of Mrg X1 induces or blocks the sensation of pain then the claimed assay lacks specific utility in currently available form.

7) Claims 57 to 61, 66 to 81, 87 to 91 and 93 to 95 are rejected under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to use the instant invention for those reasons given above with regard to the rejection of these claims under 35 U.S.C. § 101.

Further, these claims encompass a binding assay that can employ a "Mrg X1" polypeptide having other than the entire amino acid sequence presented in SEQ ID NO:16 of the instant application. It is noted that an assay that employs Mrg X1 to identify compounds that "modulate" pain is useful in such a capacity only in so far as the action of the receptor protein employed therein is predictive of the response of a protein *in vivo*. However, the instant specification does not provide the guidance needed to use the claimed process with a "Mrg X1" polypeptide comprising anything less than the

entire amino acid sequence presented in SEQ ID NO:16. The instant claims encompass an assay that employs a non-naturally occurring protein whose amino acid sequence deviates from SEQ ID NO:16 by as many as forty eight amino acid residues. The only manner of using the claimed method described in the instant specification is in the identification of compounds that "modulate" pain because they agonize or antagonize the "Mrg X1" protein described therein. The claimed invention is only useful in this capacity in so far as the "Mrg X1" protein employed therein responds in a manner that is predictive of an authentic physiological response. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), held that

> "Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

Because the instant specification does not identify those amino acid residues in SEQ ID NO:16 which are critical to the structural and functional integrity of a "Mrg X1" receptor protein comprising that sequence, identify a structurally analogous protein for which this information is known and could be applied to the instant protein by extrapolation, or

even provide a single working example of an intentionally modified "Mrg" protein of the instant invention, an artisan can not change even a single residue within the amino acid sequence of SEQ ID NO:16 and predict the effects of that change on the performance of that protein "by resort to known scientific law". Unless one can predict, with reasonable confidence, that an intentionally modified "Mrg X1" protein is going to produce a response that is predictive of a native human "Mrg X1" protein, the information obtained from a process that uses that modified protein would be of no practical value even if one identifies a specific physiological role for "Mrg X1".

8) Claims 75 to 81, 83 and 95 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description and the enablement requirements for those reasons of record as applied to claims 75 to 81 and 83 in section 6 of the previous office action. As essentially stated therein, these claims are drawn to an assay that requires a "known Mrg polypeptide agonist". Applicant indicates that the text on page 100 of the instant specification identifies several agonists that activate MrgA1. It is noted that the claimed method is limited to "Mrg X1", not MrgA1. A method encompassed by these claims that employs a "Mrg agonist" that is not an agonist of "Mrg X1" is inoperative. Therefore, the only operable embodiments of the claimed assay require a "Mrg X1" agonist, and the instant specification does not identify a single compound as a "Mrg X1" agonist. The text on page 99 of the instant specification states that "[a]lthough the *mrg*-family genes are highly homologous, the most divergent regions were the extracellular domains (see Figure 6A)" and "[t]he variability of the extracellular domains of mrg family suggests that they may recognize different ligands". Therefore,

one does not have a reasonable expectation that an agonist for Mrg A1 will agonize "Mrg X1".

9) Claims 57 to 61, 66 to 81, 87 to 91 and 93 to 95 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for those reasons of record as applied to claims 57 to 61 and 66 to 83 in section 7 of the previous office action. As stated therein, because the instant specification does not identify that property or combination of properties which is unique to and, therefore, definitive of a "Mrg polypeptide" an artisan can not determine if a compound **which meets all of the other limitations of a claim** would then be included or excluded from the claimed subject matter by the presence of this limitation. Contrary to Applicant's argument, the addition of structural limitations to the claims does not overcome this rejection.

10) Claims 57 to 61, 66 to 74 and 82 stand rejected under 35 U.S.C. 102(b) as being clearly anticipated by the Ahmad et al. patent publication (WO 99/32519, cited by Applicant), for those reasons of record in section 8 of the previous office action.

11) Applicant's arguments filed 15 July of 2004 have been fully considered but they are not persuasive.

12) **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John D. Ulm whose telephone number is (571) 272-0880. The examiner can normally be reached on 9:00AM to 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kunz Gary can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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